# General

## Guideline Title

The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses.

## Bibliographic Source(s)

Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, Lamm CI, Tracy SL, Rosenberg RS. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine clinical practice guideline. Sleep. 2012 Aug 1;35(8):1039-62. [155 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Li KK, Loube DL, Morgenthaler T, Wise M. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004 May 1;27(3):557-9.

American Academy of Sleep Medicine. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999 Nov 1;22(7):961-8. [33 references]

# Regulatory Alert

## FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

# Recommendations

## Major Recommendations

Levels of recommendation (Standard, Guideline, and Option) and levels of evidence (High, Moderate, Low, Very Low) are defined at the end of the "Major Recommendations" field.

Pharmacotherapy for Restless Legs Syndrome (RLS)

Dopaminergic Medications

*Non-ergot Derived Dopamine Agonist: Pramipexole*

Clinicians should treat patients with RLS with pramipexole. (STANDARD)

Values and Trade-Offs: Pramipexole is upgraded to standard from the previous practice parameter based on multiple studies showing efficacy in RLS. Pramipexole is typically well tolerated and side effects are self-limited with cessation of pramipexole therapy.

*Non-ergot Derived Dopamine Agonist: Ropinirole*

Clinicians should treat patients with RLS with ropinirole. (STANDARD)

Values and Trade-Offs: This recommendation is upgraded to standard from the previous practice parameter based on multiple studies with randomized controlled data (RCT) data showing efficacy in RLS therapy. Ropinirole is typically well tolerated and side effects are self-limited with cessation of ropinirole therapy.

*Levodopa*

Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor. (GUIDELINE)

Values and Trade-Offs: This recommendation is changed from the previous practice parameter, where it was given a STANDARD level of recommendation for use. Levodopa has longstanding clinical use in RLS with concomitant concerns for daytime RLS augmentation and early morning rebound of RLS symptoms. The use of levodopa may be most advantageous for those patients with intermittent RLS symptoms that do not require daily therapy. For those that require daily therapy for RLS, the newer dopaminergic agents may be a better choice. Therapy should be tailored to the individual patient's specific circumstances and needs. Vigilance for secondary impulsive behavior as an adverse reaction is needed.

*Ergot-derived Dopamine Agonists: Pergolide and Cabergoline*

Clinicians should not treat RLS patients with pergolide because of the risks of heart valve damage. (STANDARD)

Values and Trade-Offs: Pergolide risks include heart valve damage and retroperitoneal fibrosis making any future use of pergolide in RLS strongly contraindicated.

Given the potential of side effects, including heart valve damage, clinicians can treat RLS patients with cabergoline only if other recommended agents have been tried first and failed, and close clinical follow-up is provided. (GUIDELINE)

Values and Trade-Offs: The risks of cabergoline are sufficient to recommend cabergoline not be used in routine clinical practice for RLS particularly since there are multiple alternative RLS dopaminergic therapies with a better side effect profile. Because the risk is unclear, it is prudent to remain cautious with respect to recommending cabergoline.

Opioid Medications

Clinicians can treat RLS patients with opioids. (GUIDELINE)

Values and Trade-Offs: Opioid data shows clinical effectiveness in treating RLS with a low level of evidence. Side effects can include an undefined potential for abuse in predisposed patients and a possible risk for the development or worsening of sleep apnea. Therefore, patients should be clinically monitored for the development of symptoms. In general, however, this medication is very well tolerated and has a lower risk of augmentation than is seen in the dopaminergic medications.

Anticonvulsant Medications

*Gabapentin Enacarbil*

Clinicians can treat patients with RLS with gabapentin enacarbil. (GUIDELINE)

Values and Trade-Offs: This is a new recommendation from the prior practice parameter. Sufficient evidence has emerged since the last practice parameter to support gabapentin enacarbil as a guideline level for treatment in RLS therapy. Gabapentin enacarbil therapy is generally well tolerated with self-limited side effects. High level evidence is encouraging. However, this medication is relatively new, thereby warranting a conservative recommendation level of guideline at this time.

*Gabapentin*

Clinicians may treat RLS patients with gabapentin. (OPTION)

Values and Trade-Offs: Low level evidence supports use of gabapentin for RLS therapy. Pain relief with gabapentin supports consideration of gabapentin in patients with both RLS and pain. There are some concerning potential side effects which makes the balance of benefits versus harms uncertain.

*Pregabalin*

Clinicians may treat patients with RLS with pregabalin. (OPTION)

Values and Trade-Offs: Preliminary data shows therapeutic efficacy in pregabalin therapy for RLS. However, long-term follow up and published experience in pregabalin therapy for RLS is lacking. Thus, other better-studied RLS therapies should be considered before prescribing pregabalin.

*Carbamazepine*

Clinicians may treat RLS patients with carbamazepine. (OPTION)

Values and Trade-offs: This has been downgraded from GUIDELINE in the prior practice parameter to OPTION in this practice parameter. Although carbamazepine efficacy in RLS was shown in prior studies, these data are dated with no new additional supportive work. There are other RLS therapies with comparatively more supportive evidence, risk-to-benefit ratios, and clinical experience than carbamazepine. The benefits of carbamazepine therapy are closely balanced with potential adverse side effects which include sedation, liver abnormalities and, rarely, the potential suicidal ideation and behavior, and Stevens-Johnson syndrome.

Medications Acting on the Adrenergic Systems

Clinicians may treat patients with RLS with clonidine. (OPTION)

Values and Trade-Offs: Clonidine has minimal supporting data in treating RLS and carries a considerable risk for side effects. Clonidine might be considered in treating hypertension and RLS concomitantly. The risk of side effects (such as hypotension in normotensive patients) associated with clonidine in the treatment of RLS makes the benefit-to-harm ratio unclear.

Iron Supplementation

Clinicians may use supplemental iron to treat RLS patients with low ferritin levels. (OPTION)

Values and Trade-Offs: RLS therapy with iron may be effective in patients with RLS associated with low ferritin levels. Parenteral high molecular weight iron dextran therapy carries the potential for anaphylactic reaction. The parenteral infusion risk with low molecular weight iron dextran is substantially lower. Moreover, parenteral iron therapy with iron sucrose, iron gluconate, or ferumoxytol carries no anaphylactic risk. However, whenever possible, oral iron replacement is recommended. Oral supplemental iron carries fewer side effects—primarily constipation and rare cases of iron overload.

Therapies for Which No Recommendations Are Made

Refer to the original guideline document for information on those pharmacological and nonpharmacological RLS therapies for which a recommendation level could not be given secondary to either insufficient evidence to support any recommendation or because the therapy is no longer available in the U.S.

Therapies for Periodic Limb Movements of Sleep (PLMS)

There is insufficient evidence at present to comment on the use of pharmacological therapy in patients diagnosed with periodic limb movement disorder (PLMD) alone. (NO RECOMMENDATION)

Values and Trade Offs: There is insufficient evidence to comment on pharmacologic therapies in isolated PLMD. Existing data in RLS therapy does, in some cases, support some medical interventions in both RLS and PLMD. Clinical judgment must be used in any pharmacologic intervention in PLMD.

Definitions:

Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence*

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| Randomized trials | High → | Risk of bias<br>−1 Serious<br>−2 Very serious | Large effect<br>+1 Large<br>+2 Very large | High (four plus:++++) |
| | | Inconsistency<br>−1 Serious<br>−2 Very serious | Dose response<br>+1 Evidence of a gradient | Moderate (three plus:+++O) |
| Observational studies | Low → | Indirectness<br>−1 Serious<br>−2 Very serious | All plausible residual confounding<br>+1 Would reduce a demonstrated effect | Low (two plus: ++OO) |
| | | Imprecision<br>−1 Serious<br>−2 Very serious<br>Publication bias<br>−1 Likely<br>−2 Very likely | +1 Would suggest a spurious effect if no effect was observed | Very Low (one plus:+OOO) |

Final Assessments of Level of Bodies of Evidence*

High: The guideline developers are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: The guideline developers are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: The confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low: The guideline developers have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

*From Balshem H, Helfand M, Schunemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

American Academy of Sleep Medicine (AASM) Levels of Recommendations

| Final Standards of Practice Recommendations | | Overall Quality of Evidence | | | |
|---|---|---|---|---|---|
| | | High | Moderate | Low | Very Low |
| Assessment of benefit/harm/burden | Benefits clearly outweigh harm/burden | Standard | Standard | Guideline | Option |
| | Benefits closely balanced with harm/burden<br>OR<br>uncertainty in the estimates of benefit/harm/burden | Guideline | Guideline | Option | Option |
| | Harm/burden clearly outweighs benefits | Standard | Standard | Standard | Standard |

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)

## Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

## Clinical Specialty

Family Practice

Internal Medicine

Neurology

Sleep Medicine

## Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To survey and provide an evidence-based update of the literature and corresponding practice parameters in the area of the treatment of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)

## Target Population

Adult patients diagnosed with restless legs syndrome (RLS) using the International Classification of Sleep Disorders (ICSD)-2 or the International RLS Study Group (IRLS) diagnostic criteria or periodic limb movement disorder (PLMD)

## Interventions and Practices Considered

1. Dopaminergic medications
    - Pramipexole

    - Ropinirole
    - Levodopa with decarboxylase inhibitor
    - Pergolide (specifically recommended against and withdrawn from U.S. and world markets)
    - Cabergoline (not to be used in routine clinical practice for restless legs syndrome [RLS])
2. Opioid medications
3. Anticonvulsant medications
    - Gabapentin enacarbil
    - Gabapentin
    - Pregabalin
    - Carbamazepine
4. Clonidine
5. Iron supplementation
6. Non-ergot-derived dopamine agonist (rotigotine)

Note: Other pharmacological and nonpharmacological therapies for RLS and for periodic limb movement disorder, including lisuride, amantadine, talipexole, piribedil, alpha-dihydroergocryptine, benzodiazepines, valproic acid, valerian, antidepressants, accommodative strategies, sleep hygiene, behavioral and stimulation therapies, compression devices, exercise, and nutritional considerations, were considered but no recommendations were made.

## Major Outcomes Considered

- Treatment efficacy as assessed by subjective measures (International Restless Legs Syndrome Rating Scale [IRLS] and other rating scales)
- Treatment efficacy as assessed by objective measures (sleep-related parameters measured by polysomnography or actigraphy)
- Adverse effects of medications

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The literature search was performed using a combination of MeSH terms and keywords. The MeSH terms were Restless Legs Syndrome (RLS) and Nocturnal Myoclonus Syndrome. The keywords were: restless legs syndrome, periodic limb movement disorder, PLMD, sleep-related movement disorder(s), leg motor activity, myoclonic hyperkinesias, nocturnal myoclonus syndrome, RLS, periodic leg movement(s), periodic limb movement(s), sleep leg movement(s), and PLM. All therapies were searched with a start date of 11-1-1997 (6 months prior to previous search). Results on dopaminergic treatments between 11-1-97 to 11-1-2001 already covered in the 2004 update were excluded. The Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE was applied to the search. The search was performed first on August 12, 2010, and updated again on June 29, 2011, to capture the latest literature. The limits of the search were: humans, English, all adults (no pediatrics), randomized controlled trials (RCTs), and no editorials, letters, comments, or case reports. Studies on treatments for RLS with fewer than 10 subjects completing the study and for treatments of periodic leg movement disorder (PLMD) with fewer than 5 subjects completing the study were rejected. Also, studies with less than 1 week of treatment time were rejected. A total of 378 hits were obtained and supplemented by pearling.

## Number of Source Documents

The final number of articles included for all treatments with either benefit/efficacy or harm data is 126.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence*

| Study Design | Initial Quality of a Body of Evidence | Lower if | Higher if | Quality of a Body of Evidence |
|---|---|---|---|---|
| Randomized trials | High → | Risk of bias<br>−1 Serious<br>−2 Very serious | Large effect<br>+1 Large<br>+2 Very large | High (four plus:++++) |
| | | Inconsistency<br>−1 Serious<br>−2 Very serious | Dose response<br>+1 Evidence of a gradient | Moderate (three plus:+++O) |
| Observational studies | Low → | Indirectness<br>−1 Serious<br>−2 Very serious | All plausible residual confounding<br>+1 Would reduce a demonstrated effect | Low (two plus: ++OO) |
| | | Imprecision<br>−1 Serious<br>−2 Very serious<br>Publication bias<br>−1 Likely<br>−2 Very likely | +1 Would suggest a spurious effect if no effect was observed | Very Low (one plus:+OOO) |

Final Assessments of Level of Bodies of Evidence*

High: The guideline developers are very confident that the true effect lies close to that of the estimate of the effect.

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*From Balshem H, Helfand M, Schunemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

## Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Population, Intervention, Comparison, Outcome (PICO) Questions

PICO questions were developed for the review, and are summarized in Table 1 of the original guideline document.

Meta-Analysis

To compare the range of treatment options available for restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), one outcome measure was chosen for which the majority of studies presented data: the International Restless Legs Syndrome Rating Scale (IRLS). Data on other outcomes measures besides IRLS are summarized and presented in a descriptive manner for further information for the reader. Thus for medications that were studied prior to the development of the IRLS, meta-analysis was not performed. All meta-analyses were performed using MIX software. All analyses are presented using the random effects model.

The result of each meta-analysis is shown in a figure with several components in the original guideline document. Each study of the meta-analysis is identified along the left-hand column (study ID), and adjacent to it is the year of the study, treatment (exposed, "e") results, and control ("c") results. The results are expressed as "n/M/SD" corresponding to "number/mean/standard deviation." A graphical representation of the data is shown in the center of the figure. The vertical red line indicates the average response of all studies. The zero line represents no effect. The width of the red diamond at the bottom of the plot represents the standard deviation of the meta-analysis. If the red diamond does not touch the zero line, the meta-analysis results indicate that the treatment is different from zero (i.e., it has an effect). The magnitude of the effect across all studies is given by the value of the association measure along with the 95% confidence intervals.

Tables of the data used in the meta-analyses are presented in the Appendix of the original guideline document.

Quality of Evidence

The assessment of evidence quality was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. The GRADE system differs from other grading systems as each study is not only evaluated for study design and risk of bias, but, additionally, an estimate of effect is generated for each outcome. Multiple aspects of quality are assessed including study limitations, imprecision, inconsistency of results, indirectness of evidence, and likeliness of publication bias. The quality of evidence from observational studies can be adjusted by the presence of large magnitudes of effect, evidence of dose-response associations, and all plausible confounders that increase the confidence in the estimated effects. Quality refers to the confidence that the estimates of the effects are correct, and the quality rating is applied to a body of evidence and not to individual studies.

Briefly, risk of bias includes aspects of study design (randomized control trials [RCTs] versus non-randomized controlled trials or before-after trials) and conduct such as blinding, allocation concealment, large loss to follow-up, or selective outcome reporting. Imprecision refers to wide confidence intervals around the estimate of effect when there are relatively few patients and few events. Indirectness occurs when the question being addressed is different than the available evidence regarding population, intervention, comparator, or outcome. There is inconsistency when there is unexplained heterogeneity of the results. Reporting bias can occur if there is selective reporting of studies or outcomes, which may occur if the published evidence is limited to a small number of trials funded by a for-profit organization.

As a first step, all individual studies were assessed by 2 task force members for study design, and limitations to validity (bias) for each outcome of interest. RCTs were considered a higher level of evidence than observational, nonrandomized, or before-after interventional studies (see the "Rating Scheme for the Strength of the Evidence" field). Subsequently, the body of evidence for each outcome was assessed and graded, taking into account the results of the meta-analysis (if applicable) and other factors as described above. The final assessment, as defined in the "Rating Scheme for the Strength of the Evidence" field, was determined for each treatment and outcome measure.

The results are reported as evidence profiles in each section that include the number of studies, study design, limitations, inconsistency, indirectness, imprecision, and other considerations that went into the quality of evidence for each outcome of interest. Also reported are the number of patients that were studied, the overall effect that was calculated in the meta-analysis (reported as the *mean difference* [MD]), and a qualitative assessment of the relative importance of the outcome.

One reviewer extracted the data and graded the studies and another verified this compiled information.

## Methods Used to Formulate the Recommendations

Other

## Description of Methods Used to Formulate the Recommendations

The Standards of Practice Committee (SPC) developed these practice parameters based on the strength of evidence for efficacy of each therapy counterbalanced by an assessment of the relative benefits of each treatment versus the potential risks as delineated in the table in the "Rating Scheme for the Strength of the Recommendations" field. The assessment of evidence quality was performed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process. All individual studies were evaluated for study design, risk of bias, and an estimate of effect for each outcome measure. Multiple aspects of quality are assessed for bodies of evidence, including study limitations, imprecision, inconsistency of results, indirectness of evidence, and likeliness of publication bias. Bodies of evidence were assessed to be high, moderate, low, or very low.

Definitions of levels of recommendations used by the American Academy of Sleep Medicine (AASM) appear in the table in the "Rating Scheme for the Strength of the Recommendations" field. Particularly noteworthy in this table is that when harm/burden clearly outweighs benefit, a STANDARD level of recommendation against the proposed therapy is given regardless of the overall quality of evidence. Sections titled "Values and Trade-offs" appear under each individual practice parameter. The Values and Trade-offs discussion elucidates the rationale leading to each recommendation. These sections are an integral part of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system and offer transparency to the process.

## Rating Scheme for the Strength of the Recommendations

American Academy of Sleep Medicine (AASM) Levels of Recommendations

| Final Standards of Practice Recommendations | | Overall Quality of Evidence | | | |
|---|---|---|---|---|---|
| | | High | Moderate | Low | Very Low |
| Assessment of benefit/harm/burden | Benefits clearly outweigh harm/burden | Standard | Standard | Guideline | Option |
| | Benefits closely balanced with harm/burden<br>OR<br>uncertainty in the estimates of benefit/harm/burden | Guideline | Guideline | Option | Option |
| | Harm/burden clearly outweighs benefits | Standard | Standard | Standard | Standard |

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

The recommendations were critically reviewed by two outside experts, and the concerns that were raised were addressed by the Standards of Practice Committee (SPC) prior to submission to the Board. The SPC reviewed the assessments of bodies of evidence as well.

The Board of Directors of the American Academy of Sleep Medicine (AASM) subsequently approved these practice parameters.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate use of pharmacological and nonpharmacological treatments of restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)

Refer to the "Values and Trade-offs" sections under each parameter in the "Major Recommendations" section for specific information on potential benefits of individual treatments.

## Potential Harms

- *Dopaminergic medications*. While these agents confer many benefits, there are some adverse effects that should be recognized. Similar to patients with Parkinson's disease, restless legs syndrome (RLS) patients treated with dopamine agonists may develop dopamine dysregulation syndrome. These patients may exhibit an addictive pattern of dopamine replacement therapy use and/or behavioral disturbances including punding and impulse control disorders such as pathologic gambling, compulsive shopping, compulsive eating, and hypersexuality. Case reports indicate that discontinuation of the dopamine agonist results in resolution or improvement of the impulse control disorder, although these patients may be particularly susceptible to dopamine agonist withdrawal syndrome. Late development of augmentation (even after one year of continuous therapy on dopaminergic agents) remains a significant concern, and patients need to be monitored throughout therapy for this particular side effect.
- *Pramipexole*. Pramipexole is well tolerated. It has been reported that adverse events (AEs) were mild to moderate in intensity and typical for non-ergot dopamine agonists. These included nausea and somnolence, which typically decreased in frequency over time, and nasopharyngitis.
- *Ropinirole*. Ropinirole was found to be effective and generally well tolerated. The most common side effects were nausea, headache, dizziness, somnolence, and vomiting.
- *Levodopa*. Single doses of L-dopa, carbidopa, and entacapone (LCE) with up to 150 mg L-dopa were effective and also well tolerated without typical side effects such as nausea. Of note, Stalevo is on a Food and Drug Administration (FDA) watch list with concerns about possible increased risk of both prostate cancer and cardiovascular disease. Vigilance for secondary impulsive behavior as an adverse reaction is needed.
- *Cabergoline*. Cabergoline is primarily indicated in treatment of prolactinoma with associated risk of visual field loss. Cabergoline carries a comparatively much stronger risk-to-benefit ratio in prolactinoma therapy than that seen in RLS therapy. Cabergoline risks include valvular heart disease. The data seem to agree that there is valve risk, but the defined risk in each study varies by incidence and degree of valve injury. Other side effects were mostly mild and transient and included nausea, dizziness, and headache.
- *Opioids*. Side effects can include an undefined potential for abuse in predisposed patients and a possible risk for the development or worsening of sleep apnea. Therefore, patients should be clinically monitored for the development of symptoms.
- *Gabapentin Enacarbil*. The most common adverse events were somnolence and dizziness, which were mild-to-moderate in intensity, and generally remitted.
- *Gabapentin*. Gabapentin has the following potential side effects: sedation, dizziness, vision changes, and suicidal behavior and ideation.
- *Carbamazepine*. Potential adverse side effects include sedation, liver abnormalities and, rarely, the potential suicidal ideation and behavior, and Stevens-Johnson syndrome.
- *Clonidine*. In one study, side effects were frequent but were generally considered mild, and included dry mouth, decreased cognition, lightheadedness, sleepiness post dose, constipation, decreased libido, and headache. The risk of side effects (such as hypotension in normotensive patients) associated with clonidine in the treatment of RLS makes the benefit-to-harm ratio unclear.
- *Iron supplementation*. Anaphylactic symptoms are a risk. In 2009, the FDA issued a warning that anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection. The boxed warning recommends administering a test dose prior to the first therapeutic dose and observing reactions. However, it should be noted that parenteral infusion risk with low molecular weight iron dextran is lower (1 per 200,000) than that with high molecular weight iron dextran. Additionally, parenteral iron therapy with iron sucrose, iron gluconate or ferumoxytol carries no anaphylactic risk.

# Contraindications

## Contraindications

Pergolide risks include heart valve damage and retroperitoneal fibrosis making any future use of pergolide in restless legs syndrome strongly contraindicated. Pergolide has been withdrawn in the U.S. because of the risk of cardiac valvulopathy.

# Qualifying Statements

## Qualifying Statements

- These practice parameters define principles of practice that should meet the needs of most patients in most situations. These guidelines should not, however, be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding propriety of any specific care must be made by the physician, in light of the individual circumstances presented by the patient, available diagnostic tools, accessible treatment options, and resources.
- These practice parameters reflect the state of knowledge at the time of publication and will be reviewed, updated, and revised as new information becomes available.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, Lamm CI, Tracy SL, Rosenberg RS. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine clinical practice guideline. Sleep. 2012 Aug 1;35(8):1039-62. [155 references]

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

1999 Nov 1 (revised 2012 Aug 1)

## Guideline Developer(s)

American Academy of Sleep Medicine - Professional Association

## Source(s) of Funding

American Academy of Sleep Medicine

## Guideline Committee

Standards of Practice Committee

## Composition of Group That Authored the Guideline

*Committee Members*: R. Nisha Aurora, MD, Johns Hopkins University, School of Medicine, Baltimore, MD; David A. Kristo, MD, University of Pittsburgh, Pittsburgh, PA; Sabin R. Bista, MD, University of Nebraska Medical Center, Omaha, NE; James A. Rowley, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI; Rochelle S. Zak, MD, Sleep Disorders Center, University of California, San Francisco, San Francisco CA; Kenneth R. Casey, MD, MPH, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH; Carin I. Lamm, MD, Children's Hospital of NY–Presbyterian, Columbia University Medical Center, New York, NY; Sharon L. Tracy, PhD, American Academy of Sleep Medicine, Darien, IL; Richard S. Rosenberg, PhD, American Academy of Sleep Medicine, Darien, IL

## Financial Disclosures/Conflicts of Interest

All members of the American Academy of Sleep Medicine (AASM) Standards of Practice Committee (SPC) and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject.

This is not an industry supported study. The authors have indicated no financial conflicts of interest.

## Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Littner MR, Kushida C, Anderson WM, Bailey D, Berry RB, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Li KK, Loube DL, Morgenthaler T, Wise M. Practice parameters for the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep 2004 May 1;27(3):557-9.

American Academy of Sleep Medicine. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999 Nov 1;22(7):961-8. [33 references]

## Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the American Academy of Sleep Medicine (AASM) Web site .

Print copies: Available from the Department of Science and Research, American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561. Web site: www.aasmnet.org .

## Availability of Companion Documents

The following is available:

- Aurora RN; Kristo DA; Bista SR; Rowley JA; Zak RS; Casey KR; Lamm CI; Tracy SL; Rosenberg RS. Update to the AASM clinical practice guideline: "The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses." Sleep 2012;35(8):1037. Electronic copies: Available from the American Academy of Sleep Medicine Web site .

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI on May 2, 2005. The information was verified by the guideline developer on June 2, 2005. This summary was updated by ECRI Institute on May 8, 2007 following the U.S. Food and Drug Administration market withdrawal of Permax (pergolide). This NGC summary was updated by ECRI Institute on September 14, 2012. The updated information was verified by the guideline developer on October 4, 2012. This summary was updated by ECRI Institute on April 14, 2015 following the U.S. Food and Drug Administration advisory on Feraheme (ferumoxytol). This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on Opioid pain medicines.

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